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EVIDENCE FOR A DIRECT ROLE OF PHYSICAL EFFORT IN THE ETIOLOGY O--ETC(U)
JAN 78 R W HUBBARD, W T MATTHEW, R E CRISS

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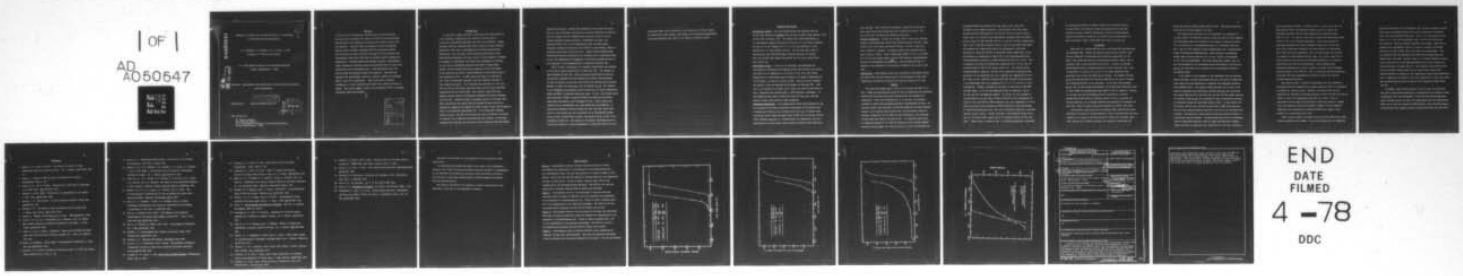

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Evidence for a Direct Role of Physical Effort in the Etiology of Heatstroke Injury and Mortality

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Key Words: hyperthermia, heatstroke injury, exertion-induced heatstroke, serum transaminases

Running Title: Exertion-Induced Heatstroke

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Abstract

A total of 171 untrained, unacclimatized and unanesthetized rats were used to evaluate the effects of sedentary and work-induced hyperthermia on the incidence of mortality and cellular injury, 24 h post-exposure. Cellular injury was defined as serum transaminase activity (SGPT and SGOT) exceeding 1000 IU/L (heatstroke levels). Both the percent mortality and the percentage of 24 h survivors with transaminase levels above 1000 IU/L were plotted against maximum core temperatures. Exertion-induced hyperthermia produced a significantly higher incidence of cellular injury and heatstroke death at lower core temperatures than hyperthermia alone. With hyperthermia only, the SGPT and SGOT dose-response curves were identical. When work was combined with hyperthermia, there was a greater incidence of elevated SGOT at lower core temperatures. These curves bore a striking resemblance to curves reflecting heat and/or work induced mortality in humans. The results suggest a direct role of physical effort in causing heatstroke injury and mortality.

Introduction

It has been a common practice to define the term 'heatstroke' as a heat disorder accompanied by the classical triad of coma or convulsions, generalized anhidrosis and fever over 106F (19). Recent reviewers (32) have cautioned that strict reliance on these arbitrary definitions could lead to underdiagnosis and unanticipated deaths. Additionally, over the years, many experienced practitioners have expressed dissatisfaction with one or more of these diagnostic criteria. For example, in 1919 Hearne (12) stated that suppression of sweating was the cause of heatstroke among British Troops in Mesopotamia; however, Willcox observed 6816 heat casualties and 555 heat deaths in the same area but did not regard anhidrosis as the primary cause of heat hyperpyrexia (37). In 1956, Austin and Berry (3) reported on 100 cases of heatstroke "selected" from over 1000 heat victims of three summer heat waves. All of them met the criterion of a hot, dry skin but even in this select population there were 39 cases whose body temperatures did not exceed 106F. More recently, there have been numerous Israeli reports of heatstroke accompanied by profuse sweating (10,33,34,35). Instead of being an uncommon variant or occurrence (22), these observations may reflect both the Israeli military practice of drinking by command in the absence of thirst as well as the role of physical effort in precipitating heatstroke (14). It is clear that strenuous physical effort, even when the external heat load is moderate, can result in excessive heat production and heatstroke (35); however, an increased metabolic heat load may not be the only factor initiating exertion-induced

heatstroke mortality. Knochel (19) reemphasized the concept that hard work in a hot environment could lead to a serious deficiency in effective arterial volume, and that profound shock would occur were it not for intense splanchnic vasoconstriction. Furthermore, by using a rat heatstroke model (13), we have demonstrated that the hyperthermia induced by working to exhaustion can be lethal to some animals, while an equivalent heat load at rest may not be. These results indicated that work-related factors contributed to an increased rate of heatstroke death at low core temperatures and suggested a heretofore unrecognized role of work, per se, in the pathophysiology of heatstroke mortality (14).

Prior to 1967, no prognostic or diagnostic significance was attached to the rise in serum enzymes noted in heatstroke (16). For example, in 1964 Leithead and Lind (23), while expressing dissatisfaction with the distinction, suggested that heat hyperpyrexia differs from heatstroke in that the patient is conscious and rational and sweating may be present. However, in 1967, both Kew et al. (16) and Shibolet et al. (33) reported on the diagnostic and prognostic value of measuring the serum transaminases (SGOT and SGPT) in suspected heatstroke cases. In fact, both groups agreed that elevations in SGOT in excess of 1000 units indicated both severe heatstroke and possibly a poor prognosis (17,32). These results were supported by two assumptions: one, that heatstroke is accompanied or preceded by widespread cellular injury; and two, that heat injury will result in the release into the circulation of the transaminase enzymes found in high concentrations in heart, and skeletal muscle, brain, liver, and kidney tissues (4). The purpose of the present investigation was to verify the elevation of serum transaminases to heatstroke levels in a rat

heatstroke model, and to determine if the incidence of cellular injury, as reflected by these enzymes, were higher with work-induced hyperthermia than with equivalent heat loads in the absence of physical effort.

Materials and Methods

Experimental Animals. The male Sprague-Dawley rats (Charles River CD strain) were obtained as prodgeny from the same breeding colony between October 1976, and March, 1977. All animals were caged individually in an environmental chamber maintained at 26°C and 49 ± 17% relative humidity and the air in this chamber (13 x 11 x 6 ft.) was replaced at a rate equivalent to 1.4 room volumes per hour. All rats were fed a diet of Charles River Chow (22% RF Rat-Mouse Formula) and water ad libitum. Rats with prefast body weights between 485 and 545 g were fasted 18-24 hours before use.

Experimental Stress. A total of 171 untrained, unacclimatized and unanesthetized laboratory rats weighing between 485 and 545 g were fasted and either run to exhaustion at 5°C (n=13), at 20, 26 or 30°C (n=57), immobilized in a restraining cage and heated at an ambient temperature of 41.5°C (n=81), or served as controls (n=20). The motor driven treadmill was similar to the one described by Pattengale and Holloszy (29). Rats ran on a 6° incline at 11 m/min, with a 2-min rest after 20 and 40 min of work. Exhaustion was achieved under a shock-avoidance contingency. It was defined as that point at which rats could not keep pace, and when placed on their backs would not right themselves.

Temperature Measurement. Core temperatures (rectal probe inserted 6.5 cm) were measured using copper/constantan thermocouples in conjunction with a thermocouple reference oven (Acromag model 340) and a 10-channel data acquisition system (Esterline-Angus model D-2020) with a teletype printout. After reaching exhaustion or a predetermined core temperature, all rats were monitored at 26°C ambient while resting in plastic cages lined with

wood shavings. After recovery and sampling, animals were returned to their cages (26°C) and allowed water but no food for 24 hours. All rats alive after 24 hours were counted as survivors.

Clinical Chemistries. As part of a larger study on the use of clinical enzymes in diagnosing heat and/or work induced disorders (15,25), venous blood (1.5 ml, tail vein) was drawn at 30 min., 24, 48, 72 and 96 hr post treatment or agonally. Pre-agonal samples were replaced with an equal volume of saline. Serum transaminases (SGOT, EC 2.6.1.1 and SGPT, EC 2.6.1.2) were assayed using a Gilford 3402 Automatic Enzyme/Endpoint Analyzer and Worthington Statzyme® kits. One International Unit is defined as the oxidation of one micromole of NADH per min at pH 7.4 and 30°C.

Calculations. Dose-response curves were estimated by the method of Read and Muench (39) and the standard error by the procedure of Pizzi (39). Significance testing was carried out by using the Student's "t" test.

Results

Post-fast body weight (mean ± S.D.) for all animals was 486 ± 12 g. Fig. 1 shows the dose-response curves for both run-exhausted and restrained-heated rats with percent mortality plotted against the maximum core temperature. These curves demonstrate: a) a continuum of increasing incidence of death with increasing severity of hyperthermia and thus, the existence within this population of both heat-sensitive and heat-resistant animals; and b) another demonstration that the hyperthermia induced by working to exhaustion can be lethal to some individuals, while enduring an equivalent heat load at rest may not be. In a previous report (14), an integrated measure of the time and intensity of core heating (degree-minutes) plotted against the percent mortality of both run-exhausted and

restrained-heated rats produced the same results with curves that converged at high thermal exposures. When elevated, the serum transaminases SGPT and SGOT peaked at 24 hours but did not return to control levels until 72 to 96 hours post experimental treatment (data not shown). Control values for SGPT and SGOT were 26 ± 6 and 84 ± 19 IU/L, respectively. Figs. 2 and 3 show dose-response curves of both run and heated rats which plot maximum core temperatures versus the percentages of rats with elevations in serum GPT and GOT to heatstroke levels (>1000 IU/L, 24 hr). The maximum core temperature at which 50% of the restrained-heated rats showed heatstroke elevations in SGPT and SGOT were both 42.1 ± 0.1C. This is slightly less than the maximum core temperature (42.4 ± 0.1C, Fig. 1) producing death in 50% of the animals within 24 h. In contrast to the restrained-heated condition, the CT50 (core temperature resulting in 50% mortality) for run-exhausted rats was a maximum core temperature of 41.8 ± 0.1C (Fig. 1) but, similarly elevated (50%) SGPT and SGOT levels occurred at correspondingly lower core temperatures of 41.7 ± 0.1 and 41.4 ± 0.1C, respectively. Finally, although the incidence of elevation in both SGPT and SGOT (Figs. 2 & 3) in restrained-heated rats is identical, this is not the case for run-exhausted animals. In contrast to the incidence of elevated SGPT in run rats (Fig. 2) which occurred at core temperatures in excess of 41C, the CT25 for SGOT elevations was a core temperature of 40.7C. Since heatstroke level elevations in SGOT occurred in a small percentage of exhausted-normothermic rats, this can be attributed primarily to exercise-induced cellular injury. Further increases in the incidence (above 40.5C, Fig. 3) of elevated SGOT, appear due to the combined effects of heat plus work. These curves, as those in Fig. 1, similarly demonstrate a continuum

of increasing incidence of cellular injury with increasing severity of hyperthermia, the existence within this population of both heat sensitive and heat resistant individuals, and that the hyperthermia induced by working to exhaustion can produce serious tissue injury in some individuals, while an equivalent heat load at rest may not.

Discussion

Heatstroke is a complex disorder with a well-described symptomatology and pathology (26). Despite the wealth of observations, however, there is still difficulty in defining exactly when body temperature is "too high", what degree and duration of hyperthermia produces injury, and, by inference, what is the associated risk (14,32). In fact, the primary physiological failure in human heatstroke is still uncertain (14). This is especially true since one or more of the classic symptoms (coma, anhidrosis and a fever over 106F) may be lacking. For example, Shibolet et al.(33) reported that 28 of 29 cases observed at the time of collapse were sweating actively, if not profusely. By the same token, Malamud et al. (26) in their classic description of 125 heatstroke fatalities noted 27 cases (22%) with temperatures below 106F (41.1°C) on admission. Because of the many host and environmental factors interacting to produce hyperthermia during military training, sports, certain occupations and living conditions, it is doubtful whether total prevention is possible (5) and, thus, there is concern that under-diagnosis is itself a risk (32).

Historically, there have been two opposing views regarding the pathophysiology of heatstroke (neural-anhidrotic versus cardiovascular) and their origins can be traced to the observations of Andral (2), Wood (38), Osler (28), Haldane (11), Adolph and Fulton (1), Fantus (7) and Drinker (6)

during the 100 year period between 1838 and 1936. With either hypothesis, shock was the critical endpoint (1,14,26).

The concept that hard work in a hot environment can predispose to a serious deficit of effective arterial volume and shock (6,7,19) combined with experimental data that indicates that working to exhaustion results in an increased rate of heatstroke mortality at low thermal loads [see Fig. 1 and ref (14)] appears to lend renewed support for a cardiovascular origin of heatstroke pathophysiology. Under different circumstances, perhaps when strenuous exercise is or is not a factor, one mechanism or the other may predominate. The points being made, however, are: (1) that the mechanism is not exclusively neural and anhidrotic and (2) work, per se, may contribute to an increased rate of heatstroke mortality at low thermal loads.

In an attempt to draw examples of this phenomenon from the existing human literature, we have recalculated data from two series of heatstroke cases where both core temperature on admission and subsequent mortality were available (8,9). The report by Gauss and Meyer (9) in 1917 on 158 cases of heatstroke from Cook County, Chicago indicates that 96 percent were males, 80% were 30 to 50 years old, and over 65% were manual laborers. In contrast, Ferris et al. (8) described 44 cases of heatstroke occurring in Cincinnati during two severe heat waves in 1936. In this series, 61% were males, 73% were over 50 years old and only 9 (20%) were doing work which at most required moderate exercise at the time of or preceding their collapse. The majority of these patients presented clinical evidence of degenerative vascular disease. If hyperthermia alone were the predominant cause of heatstroke mortality, then one might have expected a slightly higher mortality at equivalent core temperatures in the older population

with cardiovascular disease. As shown in Fig. 4, this was not the case. Approximately 30% of the heatstroke deaths occurred in younger and presumably healthier laborers with temperatures on admission below 106°F (41.1°C). In contrast, there were no deaths (at temperatures below 107°F) in the older, sedentary population. These results appear in reasonable agreement with those of Malamud on military recruits (26) where 22% of heatstroke fatalities were characterized by temperatures below 106°F (41.1°C) on admission. There is little doubt that recruits are engaged in intense physical effort since, in a recent study (27) on marine recruits, 39.2 percent had detectable myoglobin in at least one serum during the first six training days. Serum specimens with detectable myoglobin were found to contain an average creatine phosphokinase activity of over 7000 U/L. This is consistent with the observation of Knochel (20) that rhabdomyolysis coexists in nearly all cases of exertion-induced heatstroke.

The results in Fig. 2 confirm the hypothesis that the incidence of heatstroke mortality induced with or without physical effort is accompanied by evidence of cellular injury. Moreover, the results from the run-exhausted rats indicate an increased incidence of both mortality and cellular injury at lower core temperatures when work is a factor. This is particularly interesting since elevations in SGPT may indicate a damaged liver cell membrane (18,36) and a greater incidence of liver damage at comparable core temperatures in exhausted animals may suggest tissue hypoxia as a contributing factor (30).

There is good evidence to support the concept that elevations in SGOT reflect generalized cell damage. It was first found useful in diagnosing

myocardial infarction (21) and hepatitis (40) and more recently, cellular injury due to prolonged exercise (31), muscle stimulation and hypoxia (24), and acute heatstroke (14,16,33). Thus, it is interesting to note (Figs. 2 & 3) that with hyperthermia alone, the SGPT and SGOT curves are identical. This may indicate primarily liver damage. When work is combined with hyperthermia, there is a greater incidence of elevated SGOT (Fig. 3) than of SGPT (Fig. 2) at lower core temperatures. This is consistent with the hypothesis that SGOT reflects generalized cell damage better than SGPT. Finally, there is a striking similarity between these curves and the curves approximating the rate of heat and/or work induced mortality in humans (Fig. 4). This supports our contention that the rat provides a useful model for the study of heat and/or work induced disorders in humans but, more importantly, these curves demonstrate that a significant percentage of the total population, at risk, will suffer heat and work-induced injury or death at core temperatures below 106°F (41.1°C).

In summary, these results confirm: 1) that in this rat model both heat and/or work-induced heatstroke is accompanied by the release of serum transaminases into the bloodstream, 2) that exertion-induced heatstroke injury and death occurs at lower core temperatures than with hyperthermia alone, and 3) that an elevation in SGOT provides a more sensitive measure of generalized cell damage in exertion-induced heatstroke than does SGPT.

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In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences - National Research Council.

The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

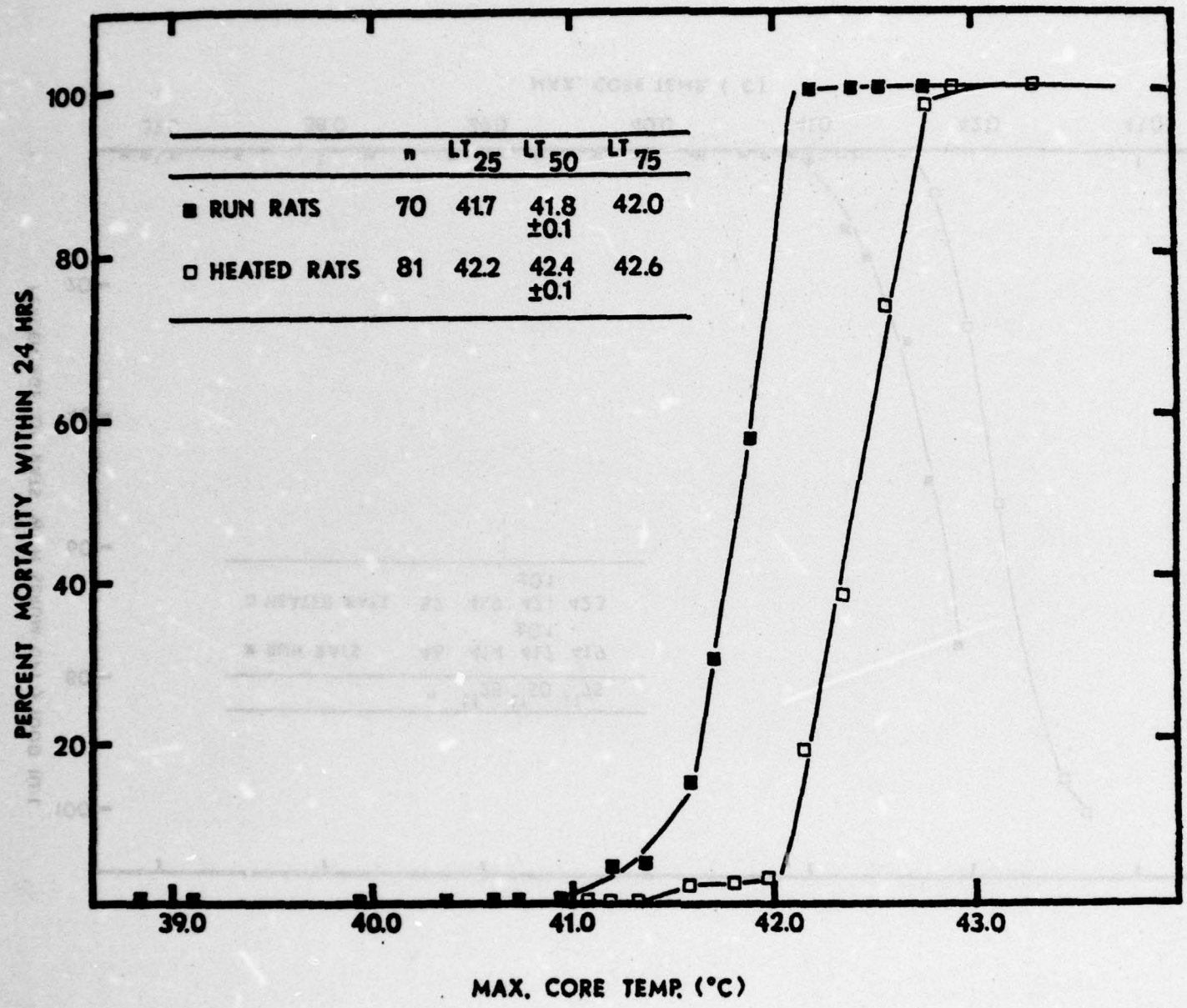
Figure Legends

Figure 1. Dose-response curves of percent mortality within 24 h versus the maximum core temperatures of run-exhausted or restrained-heated rats. Post experimental stress, the rats were removed to a recovery chamber at 26°C ambient. Water, but not food was supplied ad libitum after the core temperature returned to below 40.4°C. Values in insert represent mean ± SE of core temperatures at the indicated percent mortality. The LT50 for run rats was significantly different from the LT50 for heated rats ($p<0.005$).

Figure 2. Dose-response curves of the percentage of surviving rats with serum GPT levels in excess of 1000 IU/L versus the maximum core temperatures of run-exhausted or restrained-heated rats. Values in insert represent mean ± SE of core temperatures at the indicated percentages. The CT50 for run rats was significantly different from the CT50 for heated rats ($p<.05$).

Figure 3. Dose-response curves of the percentage of surviving rats with serum GOT levels in excess of 1000 IU/L versus the maximum core temperatures of run-exhausted or restrained-heated rats. Values in insert represent mean ± SE of core temperatures at the indicated percentages. The CT50 for run rats was significantly different from the CT50 for heated rats ($p<.025$).

Figure 4. Dose-response curves of percent mortality versus temperature on admission in human heat stroke patients. Data was recalculated by the method of Reed and Muench from the sources indicated in the insert. See text for details.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PERCENT MORTALITY WITHIN 24 HRS
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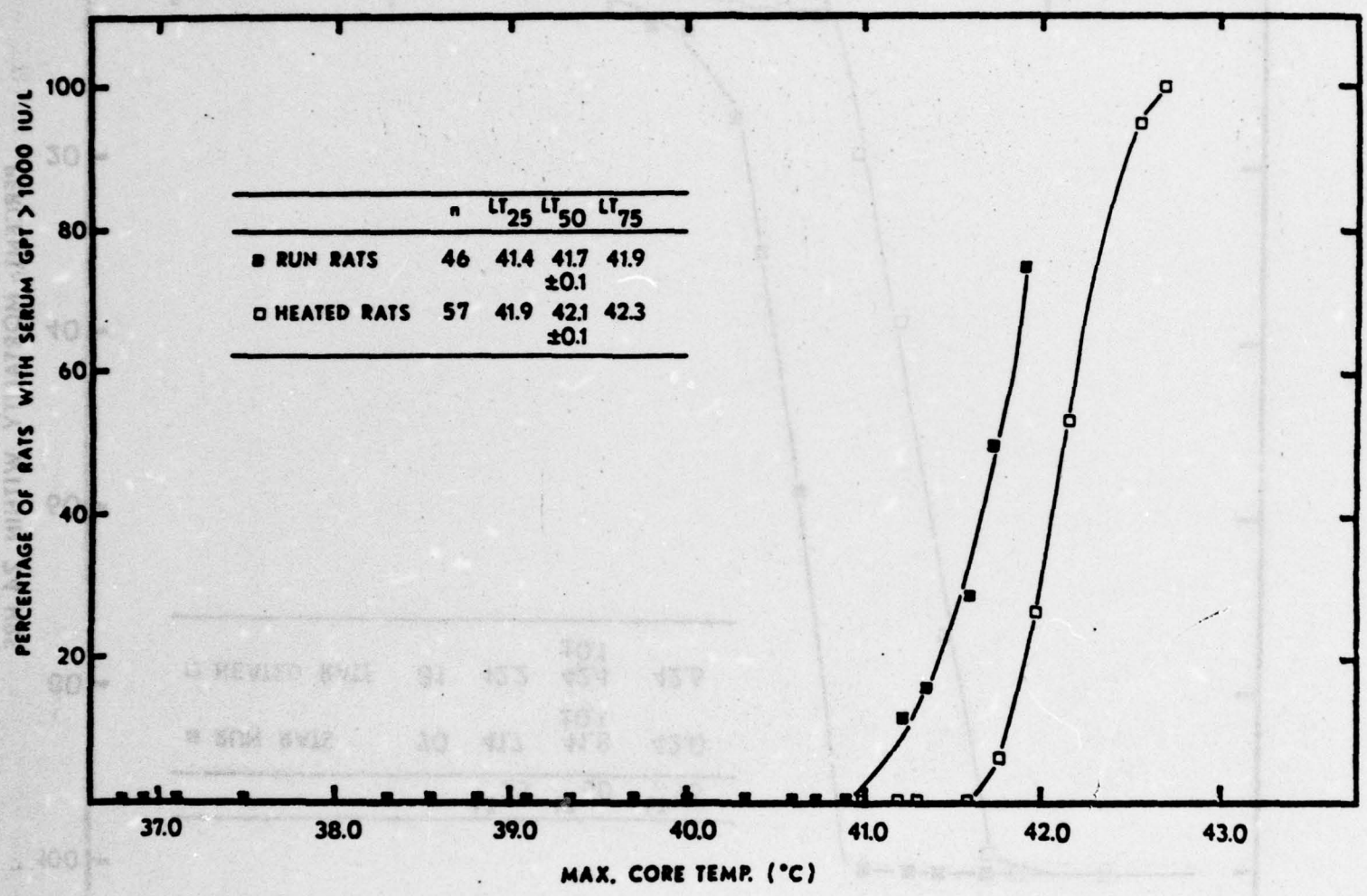
PERCENTAGE OF RATS WITH SERUM GPT > 1000 IU/L
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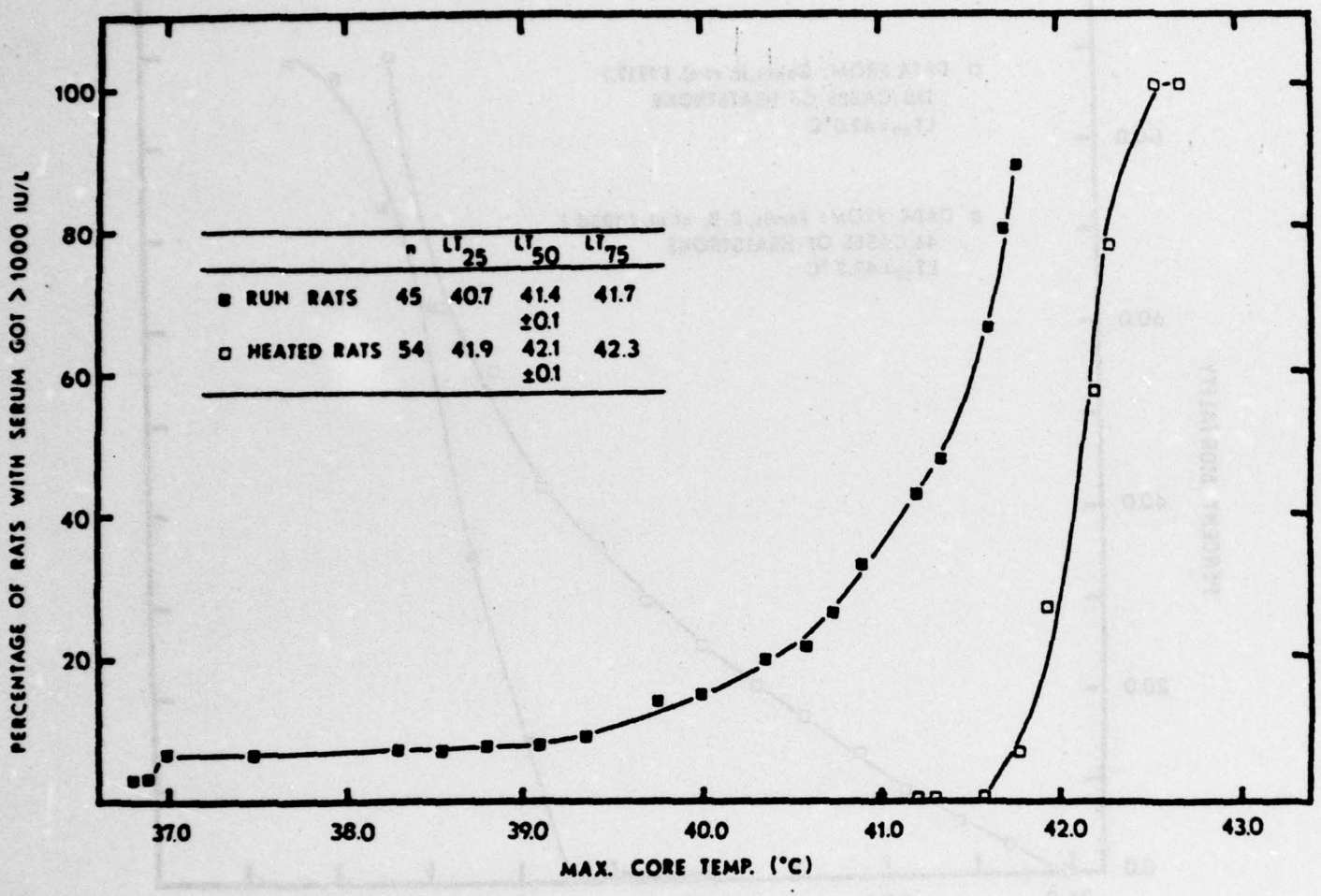
■ RUN RATS 46 41.4 41.7 ±0.1 41.9
□ HEATED RATS 57 41.9 42.1 ±0.1 42.3


PERCENTAGE OF RATS WITH SERUM GOT > 1000 IU/L
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MAX. CORE TEMP. (°C)
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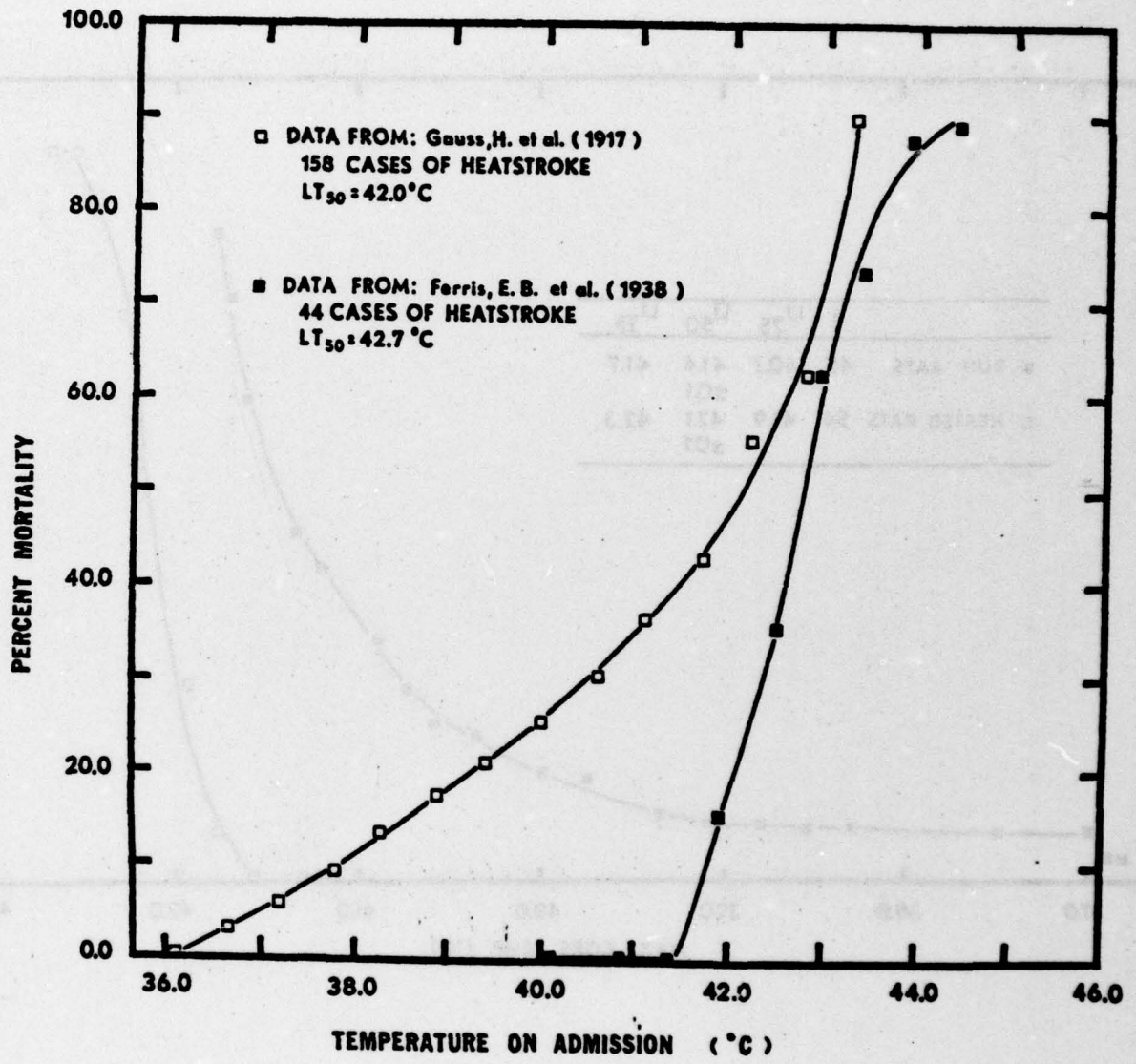
□ HEATED RATS 54 41.9 42.1 ±0.1 42.3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PERCENT MORTALITY
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46.0
TEMPERATURE ON ADMISSION (°C)
□ DATA FROM: Gauss, H. et al. (1917)
158 CASES OF HEATSTROKE
LT50 = 42.0°C
■ DATA FROM: Ferris, E. B. et al. (1938)
44 CASES OF HEATSTROKE
LT50 = 42.7 °C

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hyperthermia, heatstroke injury, exertion-induced heatstroke, serum transaminases

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

A total of 171 untrained, unacclimatized and unanesthetized rats were used to evaluate the effects of sedentary and work-induced hyperthermia on the incidence of mortality and cellular injury, 24 h post-exposure. Cellular injury was defined as serum transaminase activity (SGPT and SGOT) exceeding 1000 IU/L (heatstroke levels). Both the percent mortality and the percentage of 24 h survivors with transaminase levels above 1000 IU/L were plotted against maximum core temperatures. Exertion-induced hyperthermia produced a significantly higher incidence of cellular injury and heatstroke death at lower core

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temperatures than hyperthermia alone. With hyperthermia only, the SGPT and SGOT dose-response curves were identical. When work was combined with hyperthermia, there was a greater incidence of elevated SGOT at lower core temperatures. These curves bore a striking resemblance to curves reflecting heat and/or work induced mortality in humans. The results suggest a direct role of physical effort in causing heatstroke injury and mortality.